

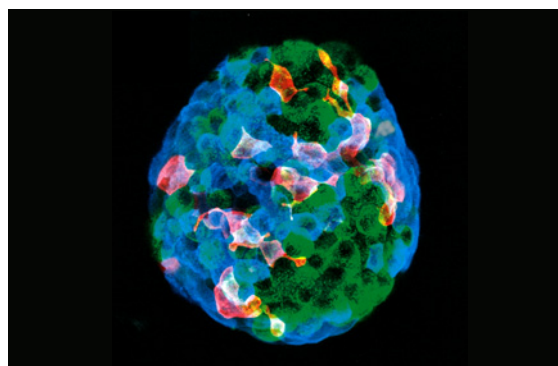
Diabetes, Endocrinology, and Metabolic Diseases

The NIDDK's support of research in the areas of diabetes, endocrinology, and metabolic diseases spans a vast and diverse range of diseases and conditions, including diabetes, obesity, osteoporosis, cystic fibrosis, lysosomal storage disorders, and thyroid and other endocrine disorders. Together, they affect many millions of Americans. As highlighted in this chapter, the past 60 years have brought about significant research progress and led to dramatic improvements in the health and quality of life of people affected by these diseases and disorders.

DIABETES OVERVIEW

Diabetes is characterized by the body's inability to produce and/or respond appropriately to the hormone insulin. Produced by beta cells in the islets of the pancreas, insulin is needed for the body to absorb and use glucose (sugar) as a cellular fuel. Defects in insulin production or action result in persistent elevation of glucose levels and other metabolic abnormalities, which can lead to development of debilitating disease complications. The most common forms of the disease are type 1 diabetes, in which the body loses its ability to produce insulin; and type 2 diabetes, which is due to a combination of insulin resistance and insufficient insulin production. Women can also develop gestational diabetes, a risk factor for type 2 diabetes, during pregnancy. Rarer forms of diabetes also exist. Diabetes affects about 23.6 million people in the U.S.; another 57 million Americans are estimated to be at increased risk for the disease.¹

Insights gained from research over the past 60 years have contributed to a knowledge base leading to improvements in survival and quality of life for people with diabetes. Doctors now use simple blood tests to diagnose diabetes and to assess long-term blood glucose control. People at high risk for type 2 diabetes can prevent or delay disease



In this pancreatic islet, beta cells, which produce insulin, are stained green; alpha cells, which produce glucagon, are blue; and delta cells, which produce somatostatin, are red.

Image credit: Dr. Todd C. Brelje and Dr. Robert L. Sorenson, Islet Biology Laboratory, Department of Genetics, Cell Biology and Development, University of Minnesota.

onset by losing a modest amount of weight through dietary changes and moderate exercise. People with type 1 diabetes can reduce their risk for complications by intensively controlling blood glucose levels. Doctors can prescribe new classes of oral drugs and combinations of drugs to treat people with type 2 diabetes. Patients can use new technologies, such as continuous glucose monitors, to manage their diabetes. As a result of these improvements, people with diabetes are living longer and healthier lives than ever before.

¹ http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf

HIGHLIGHTS OF DIABETES SCIENTIFIC ADVANCES SUPPORTED BY NIDDK OVER THE PAST 60 YEARS

IN THE 1960s AND 1970s, NIDDK-SUPPORTED RESEARCHERS:

1960: Recognized a rare form of diabetes later called “maturity-onset diabetes of the young” or MODY. MODY and neonatal diabetes mellitus are the two main forms of monogenic diabetes, which arise from a mutation in a single gene.

1965: Began research with Pima Indians, a community with the highest prevalence of type 2 diabetes in the world. Studies with the Pima Indians led to insights including identification of obesity and high levels of insulin in the blood as strong risk factors for the disease, and demonstration that children of mothers who are diabetic during pregnancy are at higher risk for obesity and diabetes than the children of nondiabetic mothers.

1967: Discovered pro-insulin. Pro-insulin is split into the hormone insulin and a molecule called C-peptide, a marker used to measure beta cell function. This discovery led to the production of biosynthetic insulin, which was the first hormone to be produced by biotechnology.

1969-1971: Identified the insulin receptor and described diseases associated with it.

1972: Reported that islet transplantation cures diabetes in rats.

IN THE 1980s, NIDDK-SUPPORTED RESEARCHERS:

1980-1989: Discovered glucose transporters and subsequently the genes that control glucose transport. Found defective glucose transport systems in people with diabetes.

IN THE 1990s, NIDDK-SUPPORTED RESEARCHERS:

1993: Proved that intensive blood glucose control reduces risk of complications of the eyes, kidneys, and nerves in people with type 1 diabetes, in the Diabetes Control and Complications Trial (DCCT). The DCCT validated the use of HbA1c tests for assessing blood glucose control.

1998: Demonstrated, through the United Kingdom Prospective Diabetes Study (UKPDS), that intensive blood glucose control reduces risk of eye and kidney complications in people with type 2 diabetes.

IN THE 2000s, NIDDK-SUPPORTED RESEARCHERS:

2002: Demonstrated, through the Diabetes Prevention Program (DPP) clinical trial, that people at risk of developing type 2 diabetes can prevent or delay disease onset and improve their blood sugar through modest improvements in diet and exercise or through the diabetes drug metformin.

2002: Determined, in a key component of the Diabetes Prevention Trial-Type 1 (DPT-1), that accurate assessment of risk for type 1 diabetes is feasible in relatives of people with the disease. DPT-1 was the prototype for the NIDDK’s current-day Type 1 Diabetes TrialNet.

2005: Showed, in the Diabetes Autoimmunity Study of the Young (DAISY), that newborns genetically vulnerable to type 1 diabetes can be identified and followed to prevent diabetic ketoacidosis.

2005: Reported, after long-term follow-up of DCCT participants, that intensive blood glucose control reduces cardiovascular complications of type 1 diabetes.

2006: With industry-supported scientists, realized the fruits of many years of research with the Food and Drug Administration (FDA) approval of the first generation of continuous glucose monitors paired with insulin pumps.

2008: Demonstrated, after 10-year follow-up of UKPDS participants, persistent reductions in eye and kidney complications, and decreased risk of heart attack and death due to any cause.

2008: Learned, from the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial, supported by the National Heart, Lung, and Blood Institute and the NIDDK, that there is not a “one-size-fits-all” approach to treating people with type 2 diabetes.

2009: Identified genes or gene regions commonly associated with diabetes in large-scale studies. Scientists have found over 40 genes for type 1 diabetes and over 30 for type 2 diabetes.

2009: Demonstrated remarkable improvements in long-term outcomes achieved with intensive glucose control in people with type 1 diabetes.

2009: Showed, with 10-year follow-up of DPP participants, that the lifestyle intervention yields long-term health rewards by reducing risk for type 2 diabetes and other heart disease risk factors.

UNDERSTANDING, PREDICTING, AND PREVENTING DIABETES

Different Forms of Diabetes and Common Links:

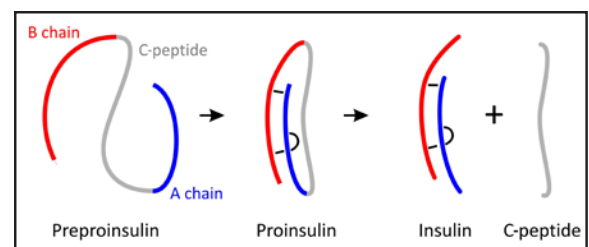
The most common forms of diabetes are type 1 and type 2 diabetes. However, there is increasing recognition of other forms of diabetes, as well as emerging evidence about common links between the two most common forms:

Monogenic forms of diabetes: Some forms of diabetes result from mutations in a single gene, such as maturity-onset diabetes of the young (MODY) and neonatal diabetes mellitus.

Gestational diabetes: A form of diabetes that is first diagnosed in women during pregnancy, gestational diabetes generally goes away after the baby is born, but leaves both mother and child at increased risk for developing type 2 diabetes.

Secondary diabetes: Secondary diabetes develops as a result of another disease or disease treatment. For example, diabetes is the most common secondary disease in people with cystic fibrosis. HIV-infected patients are at increased risk of developing diabetes when taking antiretroviral drugs. Some psychiatric medications, especially antipsychotic agents associated with substantial weight gain risk, can increase risk for obesity and diabetes.

Type 1 and type 2 diabetes—common links: Scientists are recognizing commonalities between type 1 and type 2 diabetes. Some people with type 2 diabetes have autoantibodies characteristic of type 1 diabetes. Some people with type 1 diabetes have insulin resistance, which is a hallmark of type 2 diabetes. A better understanding of these common links could inform the development of improved therapies for both forms of the disease.



The hormone insulin is formed by chemical modification and cleavage of a precursor molecule. The cleaved “C-peptide” is useful for monitoring residual beta cell function in patients with diabetes who are on insulin therapy.

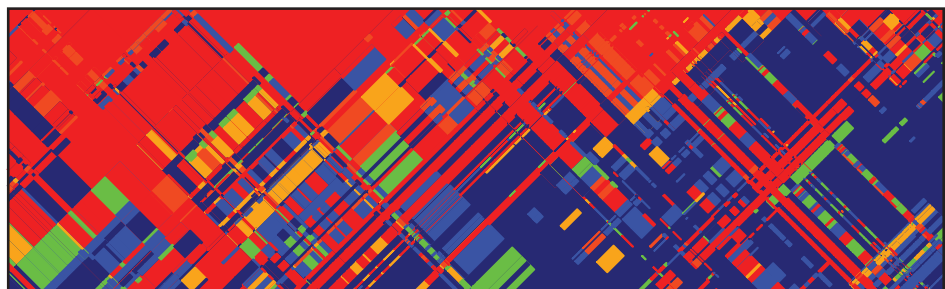
Ability to Predict Type 1 Diabetes Offers Hope for Prevention:

NIDDK-supported research on the autoimmune destruction of pancreatic beta cells in type 1 diabetes and the genetics of the disease have combined to create a powerful tool for assessing type 1 diabetes risk. Dozens of genes have now been linked to diabetes risk, most within the last 2 years, but the most important of these is *HLA*, which was linked to type 1 diabetes in the 1970s. Two of the many *HLA* variants cause substantially increased risk of the disease. Certain *HLA* variants lower risk, while others are neutral in their impact. In the 1960s, research showed that people's antibodies target their own proteins in the run-up to type 1 diabetes, signaling a high likelihood of the disease. Type 1 diabetes is an autoimmune disease, because the body attacks its own proteins and cells, so these antibodies are called autoantibodies.

With the knowledge of *HLA* and antibody associations with type 1 diabetes, NIDDK-supported scientists designed a prevention trial in the 1990s, called DPT-1, which successfully used genetic and antibody tests to predict risk for developing type 1 diabetes in people who have a close relative with the disease. Although the DPT-1 prevention strategies did not prove effective, the researchers' estimates of risk for disease based on these tests proved to be remarkably accurate. DPT-1 thus demonstrated that it is possible to identify people at risk for type 1 diabetes. Physician-scientists are now building on this knowledge and offering people with diabetes risk factors the option of participating in clinical trials to test new prevention strategies. The ability to predict risk for type 1 diabetes can speed the process of such trials by reducing the number of participants needed for the studies. In the future, clinicians will be able to use these same techniques to identify people who might benefit from any prevention approach that turns out to be effective.

Diabetes Genetics: Recent advances in genetic methods have led to an explosion in the number of genes known to be linked to the disease processes that lead to type 1 and type 2 diabetes. This diabetes genetics renaissance was made possible by the Human Genome Project, which sequenced the 3 billion nucleotide base pairs of the human genome, and began to uncover the nature and extent of human genetic variation. The HapMap, a collection of many thousands of common genetic variants throughout the genome, has been used with great success to compare people with and without different diseases and discover genes that individually may have only a modest impact on the likelihood of developing complex diseases like type 1 and type 2 diabetes. These analyses are known as genome-wide association studies (GWAS). As recently as 2003, just three type 1 diabetes genes and two type 2 diabetes genes were known. Just 6 years later, over 40 type 1 and over 30 type 2 diabetes genes or genetic regions have been identified, as a result of genome-wide studies.

As one example of a successful diabetes genetics effort, the international Type 1 Diabetes Genetics Consortium (T1DGC) has made remarkable progress in uncovering the genetic underpinnings of type 1 diabetes. With NIDDK support, the T1DGC recruited 2,800 families who have at least two siblings with type 1 diabetes and found at least 40 genetic regions associated with the disease, many of which contain genes involved in the immune system. New research is building on these exciting findings to pinpoint the exact genes that are associated with type 1 diabetes and to understand how the genes may play a role in disease.

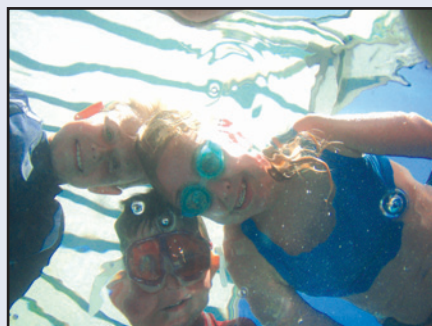


Data from a genome-wide association study of type 2 diabetes, which identified genetic sequences associated with the disease.

Image credit: From Scott LJ, et al: *Science* 316: 1341-1345, 2007. Reprinted with permission from AAAS.

Two of **Toni and Rob**

Berg's three children have type 1 diabetes, which made



the family eligible to participate in the Type 1 Diabetes Genetics Consortium study. Toni encourages other families to participate in type 1 diabetes clinical research studies, saying, "The larger the pool of people they have to study, the more they can learn about combating the disease."

Researchers have also found genes related to rarer forms of diabetes. While the risk for developing type 1 or type 2 diabetes, both common forms of the disease, is related to combinations of variants in multiple genes (as well as environmental factors), some rare forms of diabetes are "monogenic"—that is, a mutation in just a single gene can lead to the disease. In the 1990s and 2000s, NIDDK-supported researchers discovered a number of genes associated with these "monogenic" forms of diabetes, including different types of maturity-onset diabetes of the young and neonatal diabetes mellitus.

Knowledge of genes and genetic variants that contribute to different types of diabetes can lead to improved ways to predict risk for disease. Understanding the genetic contributors to diabetes can inform the development of new prevention and treatment strategies.

Environmental Contributors to Type 1 Diabetes:

Although many genes associated with type 1 diabetes have been identified, much less is known about the environmental factors that increase a person's risk of developing the disease. Thus, the NIDDK supports

research in this area. For example, since 1993, NIDDK has supported the Diabetes Autoimmunity Study of the Young (DAISY) to investigate environmental triggers of type 1 diabetes in children. As part of this study, researchers first screened blood samples to try to identify newborns at high genetic risk for the disease, as a way to facilitate subsequent analysis of potential contributing environmental factors. The DAISY study found that genetically vulnerable newborns can be identified and then followed to reduce their chances of developing a life-threatening condition called diabetic ketoacidosis and requiring hospitalization at disease onset. In 2002, NIDDK launched a large-scale study, The Environmental Determinants of Diabetes in the Young (TEDDY). This ongoing study is the first to bring together and coordinate researchers from around the world to identify triggers of type 1 diabetes. TEDDY is completing its recruitment of over 7,000 newborns at high genetic risk for the disease and will follow them until age 15. By collecting dietary and health data, and stool, blood, and other samples, scientists hope to identify a factor or factors that lead some genetically predisposed children to develop the disease while others do not. Identification of these factors will lead to a better understanding of the causes of type 1 diabetes, and may result in new strategies to prevent, delay, or reverse the disease.

Jodie Distel

enrolled her son, **Dillon**, into the DAISY study shortly after his birth. Dillon was diagnosed with type 1 diabetes at



age 7, but Jodie and Dillon were prepared for the diagnosis because of their participation in DAISY. Jodie says, "Participating in DAISY is probably the best thing I've ever done for Dillon and his future!"

Having volunteered for the DPP clinical trial and now participating in the DPP Outcomes Study, **Irish Stovall** says she would



advise anyone interested in his or her health to take part in studies like these. Although she was at high risk for type 2 diabetes at the time she enrolled in the DPP, she says “I didn’t have diabetes at that time and, thanks to the study, I still don’t.”

Type 2 Diabetes Can Be Prevented or Delayed:

Spearheaded by the NIDDK, the landmark Diabetes Prevention Program (DPP) was the first major, randomized, multisite clinical trial to demonstrate that type 2 diabetes could be prevented or delayed in a diverse American population at high risk for developing the disease. At sites throughout the country, researchers enrolled 3,234 overweight people who had impaired glucose tolerance (a condition in which blood glucose levels are elevated but not yet in the diabetic range). Nearly one-half of the participants were from minority groups disproportionately burdened by diabetes. The trial compared three preventive approaches: standard medical advice; intensive lifestyle modification aimed at losing 5 to 7 percent of body weight through diet and moderate exercise (*e.g.*, walking 5 days a week for 30 minutes a day); and treatment with the drug metformin. The duration of the intervention was approximately 3 years. The DPP results, announced in 2002, showed that the lifestyle intervention reduced risk for type 2 diabetes by a dramatic 58 percent, while metformin reduced risk by 31 percent. The interventions worked in all ethnic and racial groups studied, in both men and women, and in women with a history of gestational diabetes; and the lifestyle intervention was particularly effective in older adults. To inform the public and healthcare providers about these exciting results, the National

Diabetes Education Program (NDEP) launched the “*Small Steps. Big Rewards. Prevent Type 2 Diabetes*” educational campaign (described later in this chapter). Translational research efforts have also been initiated to develop cost-effective ways to achieve the lifestyle change that delayed or prevented type 2 diabetes (see the translational research section in this chapter).



The Diabetes Prevention Program (DPP) and the DPP Outcomes Study (DPPOS) demonstrated that people at risk of developing type 2 diabetes can prevent or delay disease onset and improve their blood sugar levels through a lifestyle intervention of modest changes in diet and exercise, and that the drug metformin also reduces risk, compared to standard therapy. In 2009, DPPOS researchers reported that, in addition to reduced risk of type 2 diabetes, people in the lifestyle group also had fewer heart disease risk factors, including improvements in blood pressure and blood lipids.

Most people who participated in the DPP continue to be followed in the DPP Outcomes Study (DPPOS). The DPPOS is examining the durability of the DPP interventions on development of type 2 diabetes and its cardiovascular complications. In 2009, DPPOS researchers reported that, after a 10-year period of following participants, long-term benefits of the interventions emerged: the lifestyle and metformin

Like many other Native Americans, **Monica Boone** has a family history of type 2 diabetes, and she was at high risk. Since participating in the DPP study, she no longer has pre-diabetes, and she says “I have more energy; I’m quicker in my movements; and I enjoy going here and there.”



interventions reduced development of diabetes by 34 percent and 18 percent, respectively. People in the lifestyle group also had fewer heart disease risk factors, despite taking fewer drugs to control their heart disease risk. Thus, even though sustaining weight loss with lifestyle changes is challenging, it produces long-term health rewards by lowering people's risk for type 2 diabetes and reducing other heart disease risk factors.

HEALTHY: The HEALTHY multicenter clinical study is collecting data on risk factors for type 2 diabetes in youth, and providing the most intensive school-based intervention to date to address the question of whether an intervention delivered only in schools can reduce overweight and obesity and other type 2 diabetes risk factors. The students in the participating middle schools are largely from minority groups disproportionately burdened by type 2 diabetes. The researchers measured risk factors for type 2 diabetes at the beginning of the study, when the children were in sixth grade. Nearly half of the students were overweight or obese, 16 percent had elevated fasting blood glucose levels, and almost 7 percent had elevated fasting insulin levels. These findings of high levels of risk factors for type 2 diabetes in middle-school age children, particularly those from minority groups, highlight the importance of focusing on this population to try to reduce these risk factors.

Diabetes During Pregnancy: Diabetes that is present during pregnancy can adversely affect both mother and child, not only during delivery and infancy, but also later in life. Among the studies the Institute has funded in this area, the University of Southern California Gestational Diabetes Mellitus (GDM) Cohort Study focused on Hispanic women who had gestational diabetes and identified metabolic factors that may predict future development of type 2 diabetes in the mother. In a groundbreaking study on the effects of the intrauterine environment on offspring, NIDDK intramural scientists, in partnership with Pima Indian volunteers, found that maternal type 2 diabetes during pregnancy increases risk for obesity and type 2 diabetes in the offspring. A similar association between maternal diabetes during pregnancy and increased risk for type 2 diabetes in the offspring was subsequently

observed in a racially and ethnically diverse population by another research team, in the SEARCH for Diabetes in Youth study. As described in this chapter, the Diabetes Prevention Program (DPP) showed that there is hope for preventing or delaying type 2 diabetes in those at high risk, including women who have had gestational diabetes.

The Gestational Diabetes Mellitus (GDM) Cohort Study focused on Hispanic women who had gestational, or pregnancy-related, diabetes. This research



has increased understanding of GDM and risk for subsequent type 2 diabetes. **Modesta Solórzano** participated in the study, and says, "It's been very helpful to me and my family." ("Ha sido muy útil para mí y para mi familia.")

Deepening the Understanding of Insulin Action and Metabolism:

Every cell in the body requires energy to perform its functions, so a key requirement for all living things is to ensure an appropriate energy supply to their tissues. The hormone insulin has long been known to regulate the body's use of glucose for energy. Secreted by the pancreas, insulin induces cells in muscle and adipose (fat) tissue to take up glucose from the blood and halts production of extra glucose by the liver; it also influences other cellular processes. In the last two decades, NIDDK-supported researchers have advanced understanding of the molecular pathways through which insulin acts and have made enormous strides in elucidating the complex network of signaling pathways through which many tissues and organs throughout the body communicate to regulate metabolism. For example, scientists have discovered that cells of the gut secrete small protein hormones in

response to the presence and absence of food. Adipose tissue is itself now recognized as an endocrine organ, releasing hormones with important effects on hunger, satiety, and metabolism. The brain, particularly a region called the hypothalamus, integrates signals from other organs and tissues to control metabolism. Indeed, the body's control of energy use and storage is becoming better understood in its remarkable subtlety and complexity.

Mouse Metabolic Phenotyping Centers

(MMPCs): The MMPCs provide phenotyping services to the research community who use mice to study diabetes, obesity, diabetes complications, and other metabolic diseases. The MMPCs use state-of-the-art technologies to offer a variety of tests that require specialized expertise or equipment and thus cannot easily be performed in individual laboratories. The Centers also support a pilot and feasibility program to develop new technologies for performing metabolic tests in mice, and several annual courses to introduce students to important techniques and theory. The MMPCs collaborate in exciting research areas, and are currently developing bariatric surgical procedures in the mouse in order to facilitate our understanding of how these surgeries benefit metabolic health as well as facilitate weight loss.

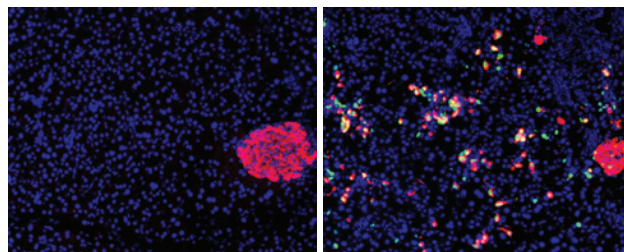
The Role of Inflammation in Diabetes:

Inflammation—tissue swelling usually accompanied by pain and heat—is the body's generic response to a host of insults, such as infection. When associated with an infection, inflammation is acute, ending when the infection is controlled. However, it is becoming increasingly clear that metabolic conditions, including diabetes and obesity, are associated with chronic inflammation in which the immune response is present but at a low and persistent level. Chronic inflammation has also been linked to insulin resistance and the development of diabetes complications. Understanding how inflammation links obesity, insulin resistance, and diabetes may lead to new therapeutic approaches. A recent multicenter, NIDDK-supported clinical trial, called Targeting Inflammation with Salsalate in Type 2 Diabetes, is testing whether an anti-inflammatory drug, called salsalate, can reduce

blood glucose levels in people with type 2 diabetes. Salsalate is approved by the FDA to relieve mild to moderate pain, fever, arthritis, and other conditions. If successful, the trial could lead to an effective, inexpensive way to treat people with type 2 diabetes.

ADVANCES IN TREATING DIABETES

Advances in Beta Cell Research: The beta cells of the pancreas produce insulin, a hormone that regulates the body's levels of blood glucose. Understanding biology of beta cells is critical for both type 1 and type 2 diabetes, as the beta cells are damaged in both forms of the disease. The Beta Cell Biology Consortium (BCBC) was established by NIDDK to promote collaborative basic research on beta cells toward the development of therapies for diabetes. BCBC investigators are studying pancreatic development, exploring the potential of stem cells as a source for making islets (clusters of cells that include beta cells) for transplantation, and determining methods to restore insulin production by regenerating a patient's beta cells. Exciting recent advances from the BCBC and from other NIDDK-supported scientists include the identification of beta cell progenitor cells and key progenitor cell proteins in the adult mouse pancreas, demonstration that some adult cells in the mouse pancreas can be reprogrammed into beta cells and that embryonic-like progenitor cells can regenerate beta cells in mice, discovery of factors important in expanding beta cell mass during pregnancy, discovery of a new marker for pre-clinical type 1 diabetes, and development of a mouse model for studying beta cell regeneration.



Increasing beta cell mass is critically important for both type 1 and type 2 diabetes. Left: Insulin-producing beta cells (pink) in a mouse pancreas. Right: Injection of an engineered virus containing regulators of pancreatic development results in additional insulin-producing cells.

Image credit: Zhou Q et al. Reprinted by permission from Macmillan Publishers Ltd: *Nature*, 455: 627-632, copyright 2008.

TREATING DIABETES—YESTERDAY AND TODAY

Since the establishment of the NIDDK in 1950, there have been major improvements in the treatment of diabetes. People with diabetes now have options for treatments that are safer and more effective, resulting in improved health outcomes. Research supported by the Institute contributed to the identification, development, and testing of many of these treatments.

TREATING DIABETES 60 YEARS AGO:

People monitored their blood glucose levels with urine tests, which recognized high but not dangerously low glucose levels and reflected past, not current, glucose levels.

People with type 1 diabetes relied on painful injections of animal-derived insulin.

People with type 2 diabetes had limited options: injections of insulin or drugs that stimulate insulin release from the beta cells of the pancreas (sulfonylureas). Both of these therapies can cause dangerously low blood glucose reactions and weight gain.

No proven strategies existed to prevent disease complications, such as blindness, kidney disease, nerve damage, and heart disease.

Physicians did not recognize the existence of rare forms of diabetes, such as maturity-onset diabetes of the young and neonatal diabetes mellitus, for which there now are specific therapies.

TREATING DIABETES TODAY:

People monitor their blood glucose with precise, less painful methods, sometimes including a continuous glucose monitor. The hemoglobin A1c (HbA1c) test is also used by patients and healthcare providers to assess average blood glucose control over the past 3 months.

People with type 1 diabetes have a choice of genetically-engineered human insulin formulations suitable for injection or use in pumps. Intensive glucose control is now possible, combining improved insulin administration with improved glucose monitoring techniques.

People with type 1 diabetes know that intensive control of blood glucose can dramatically delay or prevent eye, nerve, kidney, and cardiovascular complications, leading

to improvements in long-term outcomes, as demonstrated in the landmark, NIDDK-supported DCCT. In each successive decade, people diagnosed with type 1 diabetes are living longer than those diagnosed the decade before.

People with type 2 diabetes benefit from improved forms of insulin, a range of oral medications to control blood glucose levels and reduce the need for insulin, and drugs that may not only control blood glucose, but also strengthen the activity of a person's own insulin-producing cells.

People with type 2 diabetes benefit from intensive blood glucose control early in the course of the disease and reduce their risk of long-term complications, demonstrated by the NIDDK-supported United Kingdom Prospective Diabetes Study. However, people with type 2 diabetes at high risk of heart disease do not benefit from intensive blood glucose control below current recommendations, as shown in the NIDDK-supported ACCORD clinical trial. Thus, rather than a one-size-fits-all approach, recommendations for treating people with type 2 diabetes can be personalized.

People with diabetes can prevent many of the debilitating complications of the disease. They can reduce their risk of cardiovascular disease by controlling their blood pressure and level of low-density lipoproteins (LDL). People with nerve damage can reduce the likelihood of limb amputation with improved methods of foot care. Progression of kidney disease can be prevented with specific drugs. Laser therapy can stop progression of eye complications to blindness.

Scientists have identified rarer, specific genetic forms of diabetes, permitting improved management. For example, infants with neonatal diabetes mellitus, a disease formerly treated with insulin injections, can be better treated with oral sulfonylurea drugs, a finding based on NIDDK-supported basic research on the biology of insulin secretion.

Some people with type 1 diabetes can undergo an islet transplant to reverse insulin dependency. NIDDK supports research to improve the safety and efficacy of this treatment approach, as well as to develop an artificial pancreas that would link glucose monitoring and insulin delivery.

Metabolic Research Yields New Therapies for Type 2 Diabetes:

NIDDK research has led to the development of a remarkable new class of medications for treating type 2 diabetes. Glucose levels in the blood are controlled by a variety of factors, but two key hormones are critical. During fasting, glucagon keeps glucose levels up by signaling the liver to release stored energy. After meals, insulin has the dual effect of attenuating the glucagon effect and signaling cells to take up glucose, thus lowering its level in blood. Surprisingly, when NIDDK-supported scientists discovered the gene for glucagon in 1982, they found it was next to a gene for a different hormone—called glucagon-like peptide 1 or GLP-1—that actually acts to stimulate the insulin response after meals. GLP-1 is produced by cells of the small intestine when food is present in the digestive tract. People with type 2 diabetes do not produce enough insulin, so the capacity of GLP-1 to stimulate insulin production suggested that it might be helpful for people with the disease, but because the protein lasts just a few minutes in blood after it is produced, its potential as a therapeutic seemed limited. In the 1980s, scientists in the NIDDK Intramural Research Program discovered that saliva from a lizard known as the Gila monster contains a related but longer-lasting protein. This finding led to the development and 2005 approval of exenatide, an injected medication that boosts a person's own insulin production. Exenatide also slows digestion and makes people feel full longer after meals, leading to weight loss, a major benefit as the majority of people with type 2 diabetes are overweight or obese. However,



Exenatide, a synthetic form of a protein derived from the saliva of the venomous Gila monster, is currently being used to help manage type 2 diabetes.

Photo credit: ©2009 Photos.com.

exenatide has been found to cause acute pancreatitis (reversible but dangerous inflammation of the pancreas) in rare cases, so patients and prescribing physicians are cautioned to watch for symptoms of this complication. More recent developments include oral medications that act to extend the life of GLP-1 in the blood, yielding a similar net effect to that of exenatide without the need for injection.

Casey Burkhalter's

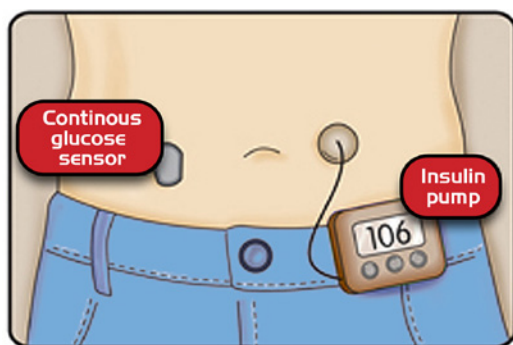
parents used to check her blood sugar every 2 hours at night, but they've been able to sleep better since



Casey began testing a continuous glucose monitor as a participant in the DirecNet study. Says her mother, **Leslie**, "This technology is unbelievably helpful."

Continuous Glucose Monitors (CGMs)—Helping To Manage the Highs and Lows of Diabetes:

For people with type 1 diabetes, undetected high or low blood glucose levels can have severe health consequences—including heart disease, blindness, and coma. As a result of decades of research, people with type 1 diabetes can now monitor their glucose levels continuously, so as to better adjust their insulin administration and take other steps to improve glucose control. Scientists invented the first device to measure blood glucose levels in the 1960s, and by the 1980s, blood glucose meters were widely used. In the 1990s, the landmark NIDDK-supported Diabetes Control and Complications Trial demonstrated the tremendous health benefits of intensive blood glucose control. This trial, which was possible because of the availability of glucose-monitoring devices, showed that intensive glucose control greatly reduced the development of diabetic eye disease, kidney disease, and nerve damage. The ongoing follow-up study recently demonstrated reduced risk for heart disease and stroke. However,



Continuous glucose monitoring can identify variations and trends in blood sugar levels over time with much greater detail than traditional finger sticks.

intensive control required multiple painful finger sticks each day to test blood glucose, and increased risk for dangerously low blood sugar. Because glucose in the blood cannot be measured continuously to detect highs and lows, scientists pursued the development of a sensor for glucose in the interstitial fluid in tissues under the skin. This research, with NIDDK, industry, and other support, led to the FDA approval of the first continuous monitor in 1999.

More advanced CGMs were approved in 2006 and 2007 for adults and children. These wearable monitors report glucose levels every 5 minutes; transmit data to an insulin pump to display real-time trend data on how levels are fluctuating; and sound alarms when levels are too high or low—especially important during sleep. Although patients still must be actively involved in determining their insulin doses, this pairing of a continuous monitor and pump has major implications. Scientists currently seek to integrate a CGM with an insulin pump so as to create an “artificial pancreas” that would automate insulin delivery in response to the body’s needs. For now, patients can improve their glucose control, with likely future health benefits, using the unprecedented knowledge from continuous glucose monitors.

Treating Type 2 Diabetes in Children:

Type 2 diabetes is increasingly being diagnosed in children, particularly minority youth. Because the disease was previously rare in children, there is little information on how best to treat it. To address this gap in knowledge, the NIDDK launched the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) clinical

trial at centers around the country, to test three different treatment regimens for type 2 diabetes in children 10–17 years of age. Through TODAY and other studies, the NIDDK hopes to ameliorate type 2 diabetes and its complications in this most vulnerable population.

After realizing from his own Internet search that he had symptoms of type 2 diabetes,

Todd Hutchinson, a

Cherokee descendant,

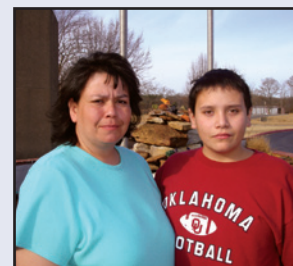
was officially diagnosed

with the disease at age 13. He then joined the

TODAY study. “I enjoy being in the study,” he

says. “It’s a little bit of work, but it’s well worth it.”

His mother, **Lisa**, adds, “The TODAY study has really changed Todd’s life.”



Studies of the Biology of Insulin Secretion Pave Way to New Treatment for Neonatal Diabetes:

In the 1950s, little did scientists know that new drugs to treat type 2 diabetes in adults would be used half a century later to treat a rare form of diabetes in babies. In the mid-1950s, sulfonylurea compounds were found to be effective for treating type 2 diabetes by stimulating insulin secretion. However, it was unknown for many decades *how* sulfonylureas worked. A clue came in 1985, when NIDDK-supported scientists demonstrated that the drug inhibited a potassium ion channel. The composition of the ion channel was revealed in 1995, when NIDDK-supported scientists discovered that the channel was made up of two proteins: the sulfonylurea receptor (SUR) and Kir6.2. Sulfonylureas bound directly to the SUR subunit of the channel to inhibit it and stimulate insulin release from the beta cell (mimicking the effects of glucose). This pioneering research contributed to a model of the regulation of insulin secretion by glucose.

In 2004, researchers in Europe found that people with permanent neonatal diabetes had mutations in their gene encoding Kir6.2. Neonatal diabetes is rare, usually occurring within the first 6 months of life, and may be permanent or transient. The same scientists discovered that 90 percent of people with permanent neonatal diabetes who had mutations in that gene could be treated with oral sulfonylurea rather than insulin—an exciting result because oral therapy is less burdensome and more effective than insulin administration for controlling blood glucose in this form of diabetes. NIDDK-supported scientists have also shown that some people with neonatal diabetes have mutations in their gene encoding SUR, and NIH-supported researchers confirmed that the gene for Kir6.2 is also linked to type 2 diabetes. Thus, the NIDDK-supported discovery of SUR/Kir6.2 informed key genetic studies and provided a greater understanding of the biology of insulin secretion. It also elegantly demonstrates how long-term NIDDK-supported basic research led to an improved treatment option for patients.

RESEARCH ON THE COMPLICATIONS OF DIABETES

The DCCT/EDIC Study Group—Improving Lives of People with Type 1 Diabetes: Impressive research progress toward combating diabetes complications was achieved through a large clinical trial launched by the NIDDK in 1983. The Diabetes Control and Complications Trial (DCCT) was a multicenter clinical trial in 1,441 people with type 1 diabetes. Completed in 1993, the trial compared the relationship between intensive versus conventional treatment of blood glucose levels and the development of small blood vessel (microvascular) complications affecting the eyes, kidneys, and nerves. The DCCT proved that intensive therapy reduces the risk of microvascular complications by 35 to 76 percent compared with conventional therapy.

Upon completion of the DCCT, the participants who had received conventional treatment were taught intensive treatment, and all of the patients were encouraged to use intensive treatment. Nearly all of

the DCCT participants volunteered for the follow-on Epidemiology of Diabetes Interventions and Complications (EDIC) study, which began in 1994. EDIC was established to assess long-term outcomes of reducing the body's exposure to high blood glucose levels. In 2002 and 2003, EDIC investigators found that, 7 to 8 years after the end of DCCT, the period of intensive glucose control during the DCCT continued to reduce risk for microvascular complications. These long-term benefits were observed despite the fact that patients from the original intensive and conventional treatment groups had nearly identical blood glucose control during EDIC. While DCCT proved that glucose control could prevent small vessel damage, the effect of glucose on cardiovascular disease (CVD) was unknown. In 2005, DCCT/EDIC researchers found that, during an average follow-up time of 17 years, people in the former intensive treatment group had fewer than half the number of CVD events than those in the conventional group. These results showed for the first time that intensive control has long-term beneficial effects on CVD risk in people with type 1 diabetes.

The discovery that intensive glucose control reduced risk of disease complications revolutionized medical care for type 1 diabetes. Physicians now recommend that patients control their diabetes as early and intensively as possible. Intensive treatment is being translated into improved health, as recently reported by scientists from the DCCT/EDIC and the NIDDK-supported Pittsburgh Epidemiology of Diabetes Complications (EDC) study. The researchers found that the outlook for people with longstanding type 1 diabetes has greatly improved in the past 20 years. This exciting finding, due in large part to the fruits of DCCT/EDIC research, is further motivation for patients to implement early and intensive blood glucose control.

Diabetes and Cardiovascular Disease:

Cardiovascular disease (CVD) is the leading cause of death for people with diabetes. Finding ways to reduce the risk of CVD in people with diabetes is a long-standing goal of NIDDK research programs, often pursued in collaboration with the National Heart,

Lung, and Blood Institute (NHLBI). There is very strong evidence that blood pressure and cholesterol control can markedly reduce CVD in people with diabetes. However, while NIDDK-supported research has clearly established the benefits of good control of blood glucose early during the course of diabetes to reduce later risk for eye, kidney, and nerve complications, the relationship of glucose control to CVD risk—particularly for people with type 2 diabetes—has proven more complex. In 2008, new insights emerged from several clinical trials. One trial, called ACCORD (supported by NHLBI with additional funding from NIDDK), showed that more intensive control than currently recommended can be dangerous in people with long-duration type 2 diabetes who also either have CVD or are at high risk of developing it. Two other non-NIH clinical trials found neither cardiovascular harm nor benefit from moving from “good” to near-normal glucose levels. However, another study, the UKPDS, which was supported in part by NIDDK, found that targeting good glucose control early in the course of disease can reduce CVD risks decades later for many people with type 2 diabetes—similar to what was seen in the NIDDK’s DCCT/EDIC study for people with type 1 diabetes. Taken together, the new results refine the approach to treating diabetes and demonstrate the importance of tailoring therapy to individual patients. Genetics also plays an important role in determining susceptibility to diabetes and its complications, and future research will continue to integrate new genetic findings into efforts to tailor therapies. Additional insights should be forthcoming from another NIDDK-supported clinical trial, called Look AHEAD (Action for Health in Diabetes), which is examining the long-term effects of sustained weight loss on CVD in obese persons with type 2 diabetes (described in the Obesity chapter).

TRANSLATIONAL RESEARCH

From Bench to Bedside: “Bench to bedside” research aims to move discoveries from a laboratory (bench) setting to a pre-clinical or clinical (bedside) setting to test new therapies. One example of a program that has fostered bench to bedside translation is the Type 1 Diabetes—Rapid Access to Intervention Development

Dan Lamb enrolled in the DCCT clinical trial in 1983, and participates in the EDIC study to this day. He says, “Had I not been part of the DCCT, I probably would not have paid attention to my diabetes as closely as I have, nor possess the same understanding of the disease and its complications that I have now. The study has been a huge part of my life, and has contributed greatly to my success as a person with diabetes.”



(T1D-RAID) program, which provides resources for pre-clinical development of drugs, natural products, and biologics that will be tested in type 1 diabetes clinical trials. When NIDDK-supported scientists demonstrated that an anti-inflammatory drug, lisofylline, prevented the recurrence of type 1 diabetes after islet transplantation in a mouse model, T1D-RAID supported the manufacture of lisofylline for human trials undertaken through the Clinical Islet Transplantation Consortium, which is co-supported by NIDDK and the National Institute of Allergy and Infectious Diseases. Fostering bench to bedside research helps to ensure a pipeline of new therapies for clinical testing.

From Clinical Study to Community and Medical Practice: Another step in the translational research spectrum is to move therapies found to be efficacious in clinical trials to the broader community. For example, the NIDDK’s Diabetes Prevention Program (DPP) clinical trial found that modest weight loss through diet and exercise reduced risk for type 2 diabetes in overweight adults with pre-diabetes. The NIDDK supports research to translate these results from a controlled clinical setting to “real world” conditions. Most of these studies involve communities with minority populations overly burdened by type 2 diabetes. Data from a recent pilot study suggest that using the YMCA to deliver a DPP

lifestyle intervention may be a low cost way to reach large numbers of people.

SPECIAL STATUTORY FUNDING PROGRAM FOR TYPE 1 DIABETES RESEARCH

The Special Statutory Funding Program for Type 1 Diabetes Research, or Special Diabetes Program, supports research on the understanding, prevention, treatment, and cure of type 1 diabetes and its complications. It is administered by the NIDDK on behalf of the Secretary of the U.S. Department of Health and Human Services and in collaboration with multiple other Institutes and Centers of the NIH and the Centers for Disease Control and Prevention (CDC). The Special Diabetes Program supports collaborative research that spans a continuum from basic research on underlying causes of disease, to pre-clinical drug development and testing, to clinical trials testing new therapies in people. The Special Diabetes Program has been extremely successful in promoting this “bench to bedside” research paradigm, which is important for moving promising therapies from the laboratory to the people who could benefit from them.

Since the Program’s inception in 1998, significant progress has been achieved. For example, an international clinical trials network, called Type 1 Diabetes TrialNet, is conducting trials testing strategies for disease prevention and early treatment. In 2009, TrialNet found that the drug rituximab preserved function of insulin-producing beta cells in people newly-diagnosed with type 1 diabetes. Rituximab targets the antibody-producing B cells of the immune system and has been approved by the FDA for treatment of B cell non-Hodgkin’s lymphoma and some autoimmune disorders. Several other trials testing novel therapies are under way through TrialNet.

Type 1 diabetes results from a complex interplay between genes and the environment, and the Special Diabetes Program supports research in these key areas. The Type 1 Diabetes Genetics Consortium (T1DGC) has identified at least 40 genetic regions associated with disease. The long-term TEDDY study has nearly

completed recruitment and is following genetically-susceptible newborns to identify environmental factors that trigger type 1 diabetes. (For information on T1DGC and TEDDY, see section on Understanding, Predicting, and Preventing Diabetes.)

Research supported by the Special Diabetes Program also contributed to the development of new continuous glucose monitoring technology. The Diabetes Research in Children Network (DirecNet) is studying the use of this technology in children. Other research supported by the Program is building on this new technology and aims to “close the loop” to link glucose monitoring and insulin delivery, toward the development of an artificial pancreas. The Special Diabetes Program also supports research on islet transplantation, beta cell biology, islet imaging, immune tolerance, diabetes complications, and other areas, toward the goals of improving the health of people with type 1 diabetes and ultimately curing the disease.

PROMOTING DIABETES EDUCATION AND INFORMATION FOR THE PUBLIC

Translating research discoveries in diabetes into education campaigns and health information that can improve public health is an important part of the NIDDK mission. The National Diabetes Education Program (NDEP), jointly sponsored by NIDDK and CDC, works in partnership with public and private organizations on efforts to improve the treatment and outcomes for people with diabetes, to promote early diagnosis, and, ultimately, to prevent the onset of diabetes. NDEP also works to reduce health disparities in diabetes by reaching out to diverse audiences. Established in 1997 to disseminate the good news from the DCCT that improved control of blood glucose levels can reduce risk for serious diabetes health complications, the NDEP has continued to evolve in response to major research findings. Currently, NDEP runs a national multicultural campaign for type 2 diabetes prevention—the first in the Nation—with tailored materials and messages for high-risk audiences. This campaign, “*Small Steps. Big Rewards. Prevent Type 2 Diabetes.*” builds on the research results of the landmark Diabetes Prevention Program, encouraging moderate weight loss through exercise and healthful

diet among people at risk for type 2 diabetes. Campaign materials include motivational tip sheets as well as print and radio public-service ads. Another national NDEP campaign, “*Control Your Diabetes. For Life,*” emphasizes the key elements of diabetes management to help prevent heart attack, stroke, and other diabetes complications. Many materials for both campaigns are available in up to 15 different languages. The NDEP has also developed special materials to help children with diabetes, their families, and school personnel deal with the daily demands of diabetes during the school year. Through its many partners, the NDEP is able to effectively develop, tailor, and disseminate materials that can help save the lives and protect the health of people with and at risk for diabetes. (For more information, visit <http://ndep.nih.gov>.)

Among the populations hardest hit by type 2 diabetes in the United States are American Indians/Alaska Natives. NIDDK, CDC, and the Indian Health Service have worked in concert with Tribal Colleges and Universities to support researchers in the development of a K–12 diabetes-related science curriculum for Tribal schools to reduce diabetes health disparities and to increase interest in the biomedical sciences and in science careers related to diabetes among American Indian children. The curriculum development was completed in 2008, and its launch was celebrated at a special ceremony at the Smithsonian’s National Museum of the American Indian.

NIDDK also provides a comprehensive diabetes resource for patients, healthcare professionals, and the general public through the National Diabetes Information Clearinghouse (NDIC). Established in 1978, the Clearinghouse develops science-based materials about diabetes and its complications, from basic information about the different forms of the disease, to easy-to-read information about signs, symptoms, prevention, management, and treatment. In carrying out its mission, NDIC works closely with NIDDK’s Diabetes Research and Training Centers; the NDEP; professional, patient, and voluntary associations; government agencies; and state health departments to identify and respond to informational needs about diabetes. To reach diverse audiences, Clearinghouse publications are increasingly made available in Spanish. Recently, the Clearinghouse

developed a special “Awareness and Prevention” series for diabetes. Part of a larger NIDDK effort designed to raise awareness of common health problems among people not yet diagnosed, the diabetes series provides brief overviews of diabetes and pre-diabetes in English and Spanish for distribution at health fairs and similar venues. As communication technology advances, NIDDK is exploring new outlets such as podcasts, vodcasts, and other approaches to increase awareness of diabetes to improve public health.



The National Diabetes Education Program includes over 200 partners at the Federal, state, and local levels working to disseminate science-based information—such as the materials shown here—to health care providers, patients, and the general public.

ENDOCRINE AND METABOLIC DISORDERS

Dramatic Advances in the Understanding and Treatment of Cystic Fibrosis: In the early 1960s, the life expectancy of a child born with cystic fibrosis (CF) was just 10 years: the disease leads to accumulation of mucus in the lungs, creating an ideal breeding ground for bacteria like *Pseudomonas aeruginosa*, that cause severe lung damage—damage that led invariably to childhood death. Research has improved prospects for people with CF tremendously since then, almost quadrupling life expectancy to 37 years in the U.S., and improving quality of life.

The landmark 1989 discovery of the CF gene, called *CFTR*, by researchers including then NIDDK-supported scientist Dr. Francis Collins (now Director

The September 8, 1989 issue of *Science* magazine featured a cover picture of



Danny Bessette,

who has cystic fibrosis (CF), and a report of the historic discovery of the CF gene. Danny has since grown and thrived, and recently graduated from college. Remarking on the progress of CF research since he was a child, he says that “the advancements they’ve made since then are incredible and help me big time.”

Photo credit: Cystic Fibrosis Foundation.

The quote from Danny Bessette is reprinted, with permission, from the Fall 2006 issue of the Cystic Fibrosis Foundation’s publication *Commitment*.

of the NIH), opened important windows into understanding of the CF disease process, which originates with mutations in the *CFTR* gene. It also suggested potential therapeutic approaches, including some, like gene therapy, that have not yet been realized. But routine newborn screening now catches cases of CF early so that therapy can begin almost from birth, thus alleviating the malnutrition and growth delays once associated with the disease. Powerful new antibiotics, like inhaled tobramycin, are effective against *P. aeruginosa*, reducing lung scarring and prolonging life. Other medications now slow the progression of lung disease, while mechanical chest physical therapy helps people with CF loosen and clear mucus from their bodies.

Life expectancy for people with CF continues to climb, but as much progress as has been made, there is still no cure. Effective treatment requires hours of demanding daily therapy. But ongoing research provides real hope for continued improvement of medical care for CF. NIDDK-supported scientists recently developed a pig model of the disease, which provides a key tool for

testing therapeutic strategies. New medications are currently in development, some of which may provide a functional CFTR protein in patients with some versions of the gene, potentially eliminating many disease complications and allowing people with the disease to live essentially normal lives. Researchers are also working to develop other new therapies with the hope of one day dramatically improving the water-salt balance in people with CF, to enable them to clear mucus from their lungs and experience fewer infections.

Strides in the Treatment of Lysosomal Storage Disorders:

The body’s cells recycle many of the substances they no longer need by digesting them with enzymes inside cellular compartments called lysosomes. Rare genetic mutations can lead to missing or defective enzymes resulting in the build-up of toxic waste products in the lysosomes. These “lysosomal storage disorders” can cause severe organ damage. In the 1960s, scientists in the NIDDK’s Intramural Research Program found that normal cells secrete lysosomal enzymes, and that cells from patients with these disorders can take them up and use them in their lysosomes. The discovery suggested the possibility that one day, people with lysosomal storage disorders could be treated with purified enzymes.

The genes for many of these enzymes were discovered in the 1980s. When dogs were found that lack some of the same enzymes, and have many of the same symptoms observed in people with these diseases, it became possible to test the enzyme replacement therapeutic strategy in an animal model. On the basis of this work, clinical trials then led to the FDA approval of enzyme replacement therapy for several lysosomal storage disorders, including mucopolysaccharidosis types I and VI, and Fabry, Gaucher, and Pompe diseases. The approach is not a cure, requires ongoing injections of replacement enzymes, and does not alleviate all symptoms, but it greatly improves quality of life for people with these diseases. NIDDK-supported researchers continue to test other treatment approaches, such as stabilizing mutant forms of the enzymes found in some patients. If shown to be safe and effective, enzyme stabilization may one day alleviate more

symptoms than enzyme replacement in people with some forms of lysosomal storage disorders.

Parathyroid, Bone, and Kidney Disease—the Calcium Connection: Through research to understand how the body regulates calcium levels, scientists have developed novel medical therapies and gained important understanding of multiple diseases. Insights into calcium regulation began in the 1960s and earlier, when scientists noticed a connection between blood calcium levels and parathyroid hormone secretion. Scientists in NIDDK's Intramural Research Program and elsewhere built on this research; among their findings was that parathyroid hormone raises calcium levels in the blood, in part by releasing calcium from bones. In 1993, with NIDDK and other support, scientists identified the gene for the master regulator of calcium levels—the calcium-sensing receptor protein, or CaSR. This protein maintains constant surveillance of blood calcium levels to regulate release of parathyroid hormone. NIDDK-supported scientists then discovered that mutations in the CaSR gene cause rare diseases in which excess parathyroid hormone plunders calcium from the skeleton, leading to bone fractures and other health problems. Another condition, severe kidney disease, is associated with low blood calcium levels, which trigger an increase in parathyroid hormone that weakens bones. Therapies for these conditions include surgery and other approaches—one of which was based on research on the CaSR. Scientists at a biotechnology company developed a novel type of drug, called a calcimimetic because it “mimics” calcium’s effect on the CaSR. In 2004, an industry-sponsored clinical trial demonstrated the drug’s effectiveness in kidney disease patients on dialysis. It is now FDA-approved as a treatment for excess parathyroid hormone resulting from kidney disease and also for parathyroid cancer. Patients are thus benefitting from years of basic and clinical research.

Research on parathyroid hormone has also led to a treatment for the devastating disease osteoporosis. The skeleton contains different types of living cells that routinely break down and re-build bone. Dietary nutrients, including calcium and vitamin D, and exercise help maintain and strengthen bones, and several medical interventions are available that can help reduce bone loss

and increase bone density. One of these interventions resulted from decades of research on parathyroid hormone. Paradoxically, chronic excesses of this hormone render bones weak from loss of calcium, while short bursts stimulate new bone growth. Building on pioneering research by NIDDK intramural scientists on parathyroid hormone, researchers at other institutions—supported by NIDDK, industry, and other sources—assessed the potential of this hormone for treating osteoporosis in clinical studies. This research culminated in the FDA approval, in 2002, of a synthetic version of parathyroid hormone for treating certain patients at particularly high risk for bone fractures.

Surprises from Research on Bones: Research continues to reveal how bones not only support the body, but also contribute to other biological processes. In recent research, NIDDK-funded scientists studying mice discovered that bone formation is inhibited by gut-derived serotonin. Altered serotonin levels have also been observed in people with a rare bone disease. Thus, serotonin action may be a target for developing new therapeutic strategies to treat osteoporosis. Another recent NIDDK-funded study brought to light an unexpected additional function for the skeleton, beyond its critical structural support for the body. In research in mice, a hormone produced by bone cells, osteocalcin, was found to regulate metabolic processes relevant to obesity and type 2 diabetes. This surprising finding may open new avenues for intervention approaches for metabolic conditions. Insights from research on bone biology and metabolism thus hold promise for continued benefits to health.

LOOKING TO THE FUTURE

As the NIDDK reflects on the past 60 years of supporting and conducting research on diabetes, endocrinology, and metabolic diseases, it is clear that the scientific progress achieved during that time period has been remarkable. Looking to the future, the NIDDK will continue to build on the landmark scientific discoveries of the past to foster new research breakthroughs. Paramount to this effort is the continued vigorous support of basic, pre-clinical, and clinical

research, as well as the development of educational materials to disseminate important new research findings to patients, their families, and healthcare providers. To inform research directions in diabetes, endocrinology, and metabolic diseases, the NIDDK will continue to solicit input from the broad scientific community through forums such as scientific workshops and conferences. In addition, strategic planning, with broad external input, will continue to guide future research directions. For example, *Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan* was released by NIDDK in 2006, and the Institute has recently undertaken a new strategic planning process to identify opportunities for all forms of diabetes. Through these

efforts, the NIDDK remains steadfast in its mission to support and conduct research to improve people's health and quality of life.



Photo credit: Getty Images.